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ARTÍCULO ORIGINAL

Development and validation of spectrophotometric and ion pair chromatographic techniques for estimation of telmisartan and hydrochlorothiazide

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ABSTRACT

Ultraviolet spectrophotometric and ion pair chromatographic methods have been developed for simultaneous estimation of telmisartan and hydrochlrothiazide from their tablet dosage form. The first method involves multiwavelength spectrophotometric estimation (Method 1) where interference due to hydrochlrothiazide at 286 nm (wavelength for estimation of telmisartan) was eliminated by recording absorbance difference at 286 nm and 308 nm whereas interference of telmisartan at 262 nm (wavelength for estimation of hydrochlrothiazide) was removed by recording absorbance difference at 262 nm and 282 nm. Linearity of the response was demonstrated by telmisartan in the concentration range of 5-35 µg/ml with a square correlation coefficient (r2) of 0.9995. Linearity of the response was demonstrated by hydrochlrothiazide in the concentration range of 3-21 µg/ml with a square correlation coefficient (r2) of 0.9992. The second method utilizes ion pair chromatography (Method 2) on a HIQ sil ODS column (250 mm length x 4.6 mm internal diameter) using methanol: 0.0025 M orthophosphoric acid (70:30 by volume pH 4.6) containing 0.1% 1-hexane sulphonic acid monohydrate sodium salt as mobile phase with UV detection at 259 nm over a concentration range of 20-120 µg/ml for telmisartan and 12.5-75 µg/ml for hydrochlrothiazide. Losartan potassium was used as the internal standard. Both the methods were applied successfully for the analysis of the two drugs from their tablet dosage form. The results of analysis were validated statistically and as per ICHQ2B guidelines. The developed methods are simple, selective and reproducible and can be applied for routine analysis of formulations containing telmisartan and hydrochlrothiazide.

KEYWORDS: Hydrochlorothiazide, Losartan Potassium, Multiwavelength Method, RP-HPLC, Telmisartan, and Validation.

1. Introduction

Telmisartan (TEL) is a angiotensin II receptor blocker. Chemically TEL is 4'-[(1,4[1]-Dimethyl-2'-propyl[2,6'-bi-1H-benzimidazole]-1'-yl)methyl]-[1,1'-biphenyl]-2-carbox- -ylic acid [1]. Several analytical methods such as difference spectrometry[2], immunoassay development 3 liquid chromatography-tandam mass sprectrometry [3-6], HPLC [7-9], micellar electrokinetic chromatographic method [10] , capillary zone electophoresis [11-12] , , linear sweep polarography [13] , are reported for estimation of TEL from their respective single dosage forms and biological fluids. Hydrochlrothiazide (HYD) chemically known as 6-Chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7- sulfonamide-1,1-dioxide, is a diuretic and is useful in the treatment of mild to moderate essential hypertension .The drug is reported in Indian

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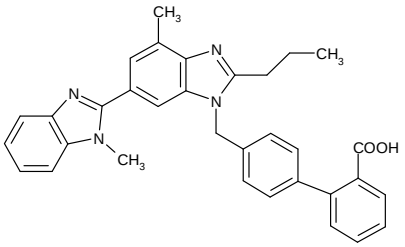
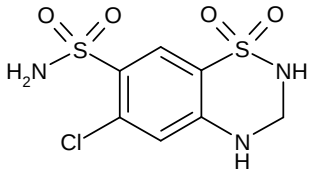
pharmacopoeia (1996), British Pharmacopoeia (1993), and United State pharmacopoeia (1995 3rd ed.) [14-16] . A survey of literature revealed different analytical methods including Gas chromatography-mass spectrometric method [17] , electrochemical method [18] , time resolved chemiluminence [19] , micellar electrokinetic method [20] , High Performance Liquid Chromatography [21-23] etc for estimation of HYD from its pharmaceutical dosage form and biological fluid. Few spectrophotometric [24-25] methods have also been reported for estimation of hydrochlorothiazide from their tablet dosage form with ramipril and Losartan (LOS). Fix dose combination containing TEL and HYD is available in tablet dosage form in market. Two methods RP- High Performance Liquid Chromatography and High Performance Thin Layer Chromatography methods are reported for the simultaneous estimation of TEL and HYD from their combined dosage forms [26-27]. In the present work an attempt has been made to develop and validate a simple, sensitive and reproducible spectrophotometric method and ion pair chromatographic method with greater precision, accuracy, and sensitivity for the quality control and routine analysis of TEL and HYD in tablet dosage form.





Telmisartan **Hydrochlorothiazide**

Chemical structure of telmisartan and hydrochlorthiazide

2. EXPERIMENTAL

2.1. Apparatus

a) A PC based Jasco V-530 recording spectrophotometer with spectral bandwidth (resolution) of 2 nm and wavelength accuracy ± 0.3 nm (with automatic wavelength correction) was employed for all measurements using a matched pair of 10mm quartz cell.

b) The HPLC system was a PC based Jasco series comprising of a pump PU-2080 and a UV-2070 detector. Manual injections were carried out using a Rheodyne injector with a fixed 20 µl external loop. The chromatographic separations were performed on a 5 µm HIQ sil ODS column (250 mm length x 4.6 mm internal diameter), operating at ambient temperature, using a mobile phase consisting of methanol: 0.0025 M orthophosphoric acid (70:30 by volume pH 4.6) containing 0.1% 1-hexane sulphonic acid monohydrate sodium salt).

c) Shimadzu AY 120 analytical balance was used for weighing.

d) PCi Ultrasonicator was used for sonication.

2.2. Materials

2.2.1. Pure samples

TEL and HYD were kindly supplied by Glenmark Ltd., Nashik and Macloide pharma Ltd., Mumbai, India. respectively. The purity given as % purity ± SD was found to be 100.65 ± 0.71 and 99.23 ± 0.82 respectively for TEL and HYD.

2.2.2. Market samples

Marketed sample of TEL and HYD (Telsar H) in their combined tablet dosage form of Merck Limited Aurangabad, India. Batch No. A 6011WB was used for analysis. Each tablet contained 40 mg of TEL and 12.5 mg of HYD.

2.2.3. Chemical and reagents

For spectrophotometric work methanol (Loba chemie Pvt. Ltd. Mumbai, India) of spectroscopic grade was used. For HPLC work double distilled water was prepared in laboratory. Methanol, Orthophosphoric acid and 1-hexane sulphonic acid monohydrate sodium salt (Loba chemie Pvt. Ltd. Mumbai, India) of HPLC grade were used.

2.3. Preparation of standard and sample solutions

2.3.1. Standard stock solutions

For spectrophotometric method standard stock solutions of TEL and HYD (1000 µg/ml each of TEL and HYD) were prepared by weighing accurately 100 mg of TEL and HYD separately into two 100 ml volumetric flasks and dissolved in 40 ml of methanol. The mixture was sonicated for 10 minutes and volume was made up to 100 ml with the same solvent.

For HPLC method standard stock solutions containing TEL was prepared by transferring 100 mg of TEL into 50 ml volumetric flask. It was then dissolved in 30 ml of methanol, ultrasonicated for 10 minutes and the final volume of the solution was made up to 50 ml with methanol to get stock solution containing 2000 µg/ml of TEL. 50 mg of HYD was separately weighed and transferred into another 50 ml volumetric flask. It was dissolved in 40 ml methanol and ultrasonicated for 10 minutes. The final volume of the solution was made up to 50 ml with methanol to get stock solution containing 1000 µg/ml of HYD.

LOS was selected as an internal standard. Standard stock solution containing LOS was prepared by dissolving 5 mg of LOS in 40 ml of methanol in a 50 ml volumetric flask. It

was then ultrasonicated for 10 minutes and then final volume of solution was made up to 50 ml with methanol to get 100 µg/ml of LOS.

2.3.2. Working solutions

From the stock solutions 1 ml of the TEL and HYD standard stock solution were transferred in two separate 100 ml volumetric flasks and diluted to the mark with methanol to get a final concentration of 100 µg/ml each of TEL and HYD for the spectrophotometric work.

For HPLC method, 50 ml of the Standard stock solutions containing TEL was transferred into separate 100 ml volumetric flask and 10 ml of HYD were transferred into separate 100 ml volumetric flasks and diluted to the mark with methanol to get a final concentration of 1000 µg/ml of TEL and 100 µg/ml HYD.

2.4. Laboratory prepared mixtures

2.4.1. For calibration curve of spectrophotometric method

Accurate aliquots of TEL and HYD were transferred from working solutions (100 µg/ml) into a series of seven 10 ml volumetric flasks and volume was made up to the mark with methanol. Seven mixed standard solutions containing concentrations of 5-35 µg/ml of TEL and 3-21 µg/ml of HYD were obtained.

2.4.2. For calibration curve of HPLC method

In to a series of six 10 ml volumetric flasks, appropriate aliquots from working solutions of TEL (1000 µg/ml) and HYD (100 µg/ml) were pipetted and to each flask 2 ml of (100 µg/ml) LOS as internal standard was added and then final volume of all the solutions was made up to 10 ml with methanol. Six mixed standard solutions containing 20-120 µg/ml of TEL and 12.5-75 µg/ml of HYD with each mixed standard containing 20 µg/ml of LOS were obtained.

2.5. Procedures of Analysis

2.5.1. For multiwavelength method

2.5.1.1. Linearity

Absorption spectras of seven mixed standard solutions prepared as above were recorded in the range of 200-400 nm with scanning speed of 1000 nm/min**,** 1.0 nm data pitch and 2 nm bandwidth against methanol as blank. Calibration curve for TEL was constructed against concentration by taking absorbance differences at 286 and 308 nm from the spectra of mixed standards whereas the calibration curve for HYD was constructed against concentration by taking absorbance differences at 262 and 282 nm. The data of regression

equations is given in table 8.

2.5.1.2. Assay of laboratory-prepared mixtures

Absorption spectras of different laboratory-prepared mixtures containing different concentrations of the two drugs were recorded. For the determination of concentration of the TEL absorbance difference was recorded at 286 and 308 nm whereas for determination of concentration of HYD absorbance difference was noted at 262 and 282 nm. The concentration of each drug was calculated from the corresponding regression equation. The results of analysis (n = 9) are given in Table 1.

2.5.1.3. Assay of marketed pharmaceutical preparation (Telsar H tablet)

A commercially available tablet formulation containing TEL 40 mg and HYD 12.5 mg was analyzed using this method. Twenty tablets were accurately weighed and average weight was calculated. These tablets were ground to a fine powder and an accurately weighed tablet powder equivalent to 10 mg of TEL was transferred to a 100 ml volumetric flask and to this 6 mg of pure HYD was added. 60 ml of methanol was added to the flask. The solution was then sonicated for 10 min at 25 ^{0}C, filtered through whatmann filter paper No.41 and the volume was made up to 100 ml with methanol. The solution was analysed using the method described under assay of laboratory-prepared mixtures (as in 3.5.1.2.**)**.

2.5.2. For HPLC method

2.5.2.1. Linearity

The mixed standard solutions as prepared above (3.4.2.) were run on chromatographic system. A 20 µl of sample solution was injected into the chromatographic system using fixed volume loop injector and chromatograms were recorded. The flow rate was maintained at 1 ml/min at ambient temperature and all the elluents were monitored at 259 nm. The separation was done on a C18 column using methanol: 0.0025 M orthophosphoric acid (70:30 by volume pH 4.6) containing 0.1% of 1-hexane sulphonic acid monohydrate sodium salt. Calibration curves for both TEL and HYD were plotted against concentration by calculating response factor at 259 nm and the corresponding regression equations were generated. The overlain chromatograms are represented in Fig. 8 and the data of regression equations is given in table 8.

2.5.2.2. Analysis of laboratory-prepared mixtures

Chromatograms of different laboratory-prepared mixtures containing different concentrations of the two drugs were recorded. The similar chromatographic conditions were applied for each laboratory-prepared mixtures and the concentrations of TEL and HYD were calculated by substituting in the regression equations. The results of analysis (n = 9) are reported in table 4.

2.5.2.3. Analysis of marketed pharmaceutical preparation (Telsar H tablet)

From the triturate of 20 tablets, an amount equivalent to 40 mg of TEL and 12.5 mg of HYD was weighed, transferred to a 25 ml volumetric flask and dissolved in 20 ml methanol. It was then ultrasonicated for 10 minutes. The solution was filtered through 0.22 µ membrane filter and then final volume of the solution was made up to 25 ml with methanol. Appropriate aliquots within the Beer's law limit were withdrawn into 10 ml volumetric flasks and to each of them 2 ml of (100 µg/ml) LOS was added as internal standard. The volume was made up to the mark with methanol and analyzed by the proposed method using the procedure described above (3.5.2.2.). The concentration of TEL and HYD present in the sample solution was calculated by using regression equation generated from calibration curve of respective drugs. The results of analysis (n = 9) are reported in table 4.

3. Results and Discussion

The development of an analytical method for simultaneous estimation of drugs without previous chemical separation in multicomponent pharmaceutical formulations has received considerable attention in recent years because of its importance in quality control of drugs and drug products.

This work is devoted for the analysis of TEL and HYD which is available together in the form of tablets. Therefore the aim of this work was to develop simple analytical methods for the simultaneous determination of TEL and HYD. This was achieved by development of one multiwavelength spectrophotometric and one ion pair chromatographic method.

3.1. Spectrophotometric method (Method 1)

Multiwavelength absorption spectrophotometric method was developed for analysis of TEL and HYD. The method utilizes seven mixed standard solutions involving scanning at 286, 308, 262 and 282 nm as sampling wavelengths. From the overlain spectra of two drugs (Fig. 1) it was noted that there is no wavelength over the scanning range of 200 to 400 nm where TEL can be accurately quantified without substantial interference of HYD. Thus quantification of TEL was achieved by taking the absorbance difference at 286 and 308 nm. Similarly there is no wavelength over the scanning range of 200 to 400 nm where HYD can be accurately quantified without substantial interference of TEL. Thus quantification of HYD was achieved by taking the absorbance difference at 262 nm and 282 nm. Overlain spectra of individual drugs and mixed standards are shown in Fig. 1 and 2.

The results of quantitative determination of TEL and HYD in tablets were found in good agreement with the labeled amount of both the drugs (Table 1). % Relative standard deviation for the determination of TEL and HYD was found to be 1.05 and 1.04. Regression analysis for multiwavelength spectrophotometric method (Table 8), the linearity of the calibration graph (Fig. 3 and 4) and adherence of the method to Beer's law was confirmed by high value of the square correlation coefficient (r^2), 0.9995 and 0.9992 for TEL and HYD respectively.

Closeness of the amount found to the labelled amount and the low coefficient of variation value showed that the proposed method was accurate and precise. Spiking Accuracy of analysis was determined performed a recovery study conducted by the proposed spectrophotometric method by performing recovery studies by spiking different concentrations of pure drug in the pre-analyzed tablet sample. The results of the recovery analysis are represented in Table 2. High recoveries obtained as 100.40 ± 0.83 and 99.53 ± 0.67 (% recovery ± standard deviation) with low standard deviation confirmed the suitability of the proposed method for the determination of TEL and HYD respectively in tablet formulation.

3.2. Ion pair chromatographic method (Method 2)

An Ion pair chromatographic method was developed for estimation of TEL and HYD which can be conveniently employed for routine quality control in pharmaceutical dosage forms. The chromatographic conditions were optimized in order to provide a good performance of the assay. To achieve the simultaneous elution of the two components under isocratic condition, different chromatographic conditions (organic modifier, flow rate, ionic strength, pH) were investigated. RP-HPLC system consisting of HIQ sil ODS column (250 mm length x 4.6 mm internal diameter) provided good resolution for separation of TEL and HYD. Mobile phases containing methanol alone or acetonitrile alone were found to elute the two compounds unresolved. Various ratios of Methanol: acetonirtrile: water was found to produce the chromatograms with very close retention times and poor resolution. Mobile phase consisting of methanol:water (70:30 by volume) separated the two components but produced tailing effect with a broad peak of TEL. Best resolution was achieved at the mobile phase composition of methanol: 0.0025 M orthophosphoric acid (70:30 by volume pH 4.6) containing 0.1% 1-hexane sulphonic acid monohydrate sodium salt where the peaks of telmisartan and hydrochlorothiazide were clearly resolved with sharp peaks of both the drugs. Losartan potassium (LOS) was used as internal standard. It was found to be a suitable internal standard for this study under the selected chromatographic conditions.

Flow rate of 0.5 ml/min. resulted in greater retention times and 1.2 ml/min. resulted in very close retention times with poor resolution. A flow rate of 1 ml/min. resulted in elution of all drugs within 10 minutes with retention times of 2.77, 4.93, 6.82, for HYD, LOS and TEL respectively. Chromatogram of laboratory prepared mixture is shown in Fig.5 while optical characteristics are shown in Table 8.

The sampling wavelength was selected after scanning the drug solutions in the mobile phase having concentration of 25 µg/ml in the UV range of 200 – 400 nm on a UV spectrophotometer. 259 nm was selected as suitable wavelength for estimation. A six-point calibration curve was constructed with working standards and was found linear as shown by correlation coefficient (r^2) ≥ 0.9973, 0.9986 for TEL and HYD respectively over their calibration ranges (Fig. 9 and 10). The results of tablet analysis show that the method was specific, as none of the excipients interfered with the analytes of interest (Fig. 6). The method was thus suitably employed for assaying the commercial formulation containing TEL

and HYD.

The proposed method was applied to the determination of TEL and HYD in their pharmaceutical dosage form. The results indicate satisfactory accuracy and precision of the method. The statistical data obtained after replicate determinations (n = 9) is shown in Table 4. The % recovery ± S. D. (n = 9) of the added TEL and HYD (Fig. 7) was found to be 101.22 ± 1.08 and 101.73 ± 1.06, respectively (Table 5).

3.3. Method Validation

Both the methods were validated for precision, accuracy, repeatability, limit of detection and limit of quantitation as per ICHQ2B guidelines and also statistically. The precision and accuracy were determined with standard quality control samples (in addition to calibration standards) prepared in triplicates at different concentration levels covering the entire linearity range. Precision is the degree of repeatability of an analytical method under normal operational conditions. The precision of the assay was determined by repeatability (intra-day) and intermediate precision (inter-day) and reported as %R.S.D. The intermediate precision was studied by comparing the assays on two different days and the results documented as standard deviation and %R.S.D. Accuracy is the percent of analyte recovered by assay from a known added amount. Accuracy of analysis was determined by performing recovery studies by using spiked concentrations of pure drug in the pre-analyzed tablet sample solution. Data from nine determinations over four concentration levels covering the specified range was determined. Results of inter-day and intra-day precision of method 1 and method 2 are given in table 3 and 6 respectively.

The limit of detection (LOD) is defined as the lowest concentration of an analyte that an analytical process can reliably differentiate from background levels. The limit of quantitation (LOQ) is defined as the lowest concentration of the standard curve that can be measured with acceptable accuracy, precision and variability. The LOD and LOQ were calculated as (Given in Table 7), LOD = 3.3σ/ S, and LOQ = 10σ/ *S*, Where σ is the standard deviation of the lowest standard concentration and *S* is the slope of the calibration curve. An appropriate number of blank samples (9 determinations) were scanned in the selected range and the standard deviations of these responses were calculated. Low LOD and LOQ for TEL and HYD respectively for both the methods shows the high sensitivity of the method.

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